

REMARKS

Upon entry of this amendment, claims 1 and 4-20, 22-26, 32-82, and 84 will be pending in the application. Claim 84 is added. Claims 2 and 3 were previously canceled. Claims 21, 27-31, and 83 are canceled herein without prejudice to prosecution thereof at a later date. Claims 1, 4-13, 22-24, 26-29, 68, 70, and 72-83 are rejected. Claims 14-20, 25, 32-67, 69, and 71 are withdrawn from consideration. Claim 23 is amended. No new matter has been introduced.

Preliminarily, Applicants note with appreciation rejoinder of claims 22 and 26 for consideration. Applicants further note with appreciation the Examiner's confirmation of the nonfinality of the present Office Action as noted on page 10 of the Action during a teleconference with the undersigned on August 5, 2004.

Claims 1 and 4-13 are patentable over the Cerniglia and LaVoie references.

Claims 1 and 4-13 are rejected under 35 U.S.C. § 102(b) for alleged anticipation, or in the alternative, under 35 U.S.C. § 103 for alleged obviousness over Cerniglia *et al.* (*Appli. Environ. Microbiol.* 56:661-668, (1990)) ("the Cerniglia reference") or LaVoie *et al.* (*Carcinogenesis*, 6(10):1483-1488 (1985) ("the LaVoie reference")). Applicants disagree with the rejections

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Alternatively, to establish a *prima facie* case of obviousness, three requirements must be satisfied: first, there must be some suggestion or motivation to modify the reference or to combine the reference teachings; second, there must be a reasonable expectation of success for achieving the claimed invention and its particular results; and, third, the prior art references must teach or suggest all the claim limitations. See *In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). In making a rejection for alleged obviousness, the initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. MPEP § 2142. "To support the conclusion that the claimed invention is directed to

obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte* Clapp, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985).

The Office action asserts that claims 1 and 4-13 are readable on fungal cells. The present claims, however, are not broadly directed to fungal cells but are tailored to claims encompassing yeast and plant cells. The Cerniglia reference describes analysis of the metabolism of methylated anthracene chemicals by the fungus *Cunninghamella elegans*. As the Cerniglia reference does not teach either expressly or inherently a mutagenic effect of anthracene and its derivatives on yeast or plant cells, the reference does not anticipate the present claims. In addition, no reasoning establishing the obviousness of a mutagenic effect on yeast cells in view of the disclosure of the Cerniglia reference has been provided. Indeed, Applicants respectfully submit that the Cerniglia reference has no bearing on the present claims. Because the Cerniglia reference does not teach or suggest a method for making hypermutable yeast or plant cells *in vitro* by exposing such cells to anthracene derivatives, claims 1 and 4-13 are patentable over that reference. Accordingly, Applicants respectfully request withdrawal of the rejection.

Similarly, the LaVoie reference is directed to a mutagenic effect in the bacteria *Salmonella typhimurium*. The reference neither teaches nor suggests a mutagenic effect of anthracene or its derivatives on yeast or plant cells. Thus, claims 1 and 4-13 are patentable over that reference. Withdrawal of the rejection is respectfully requested.

Claims 1, 4-13, 22, 23, 26, 68, and 72-83 are patentable over the Euler reference.

Claims 1, 4-13, 22, 23, 26, 68, and 72-83 are rejected under 35 U.S.C. § 103 over Euler (CAPLUS Database, AN: 1948:32360, abstract only) ("Euler" or "the Euler reference"). Applicants respectfully disagree with the rejection.

Claims 1 and 4-13 are directed to methods for generating a hypermutable plant or yeast cell by exposing the cell to a chemical inhibitor of mismatch repair. "Hypermutable" is defined in the specification as the state in which a cell is made more susceptible to mutation through a loss or impairment of the mismatch repair system. (Specification at page 10, lines

9-10.) Similarly, claims 72-82 and 84 recite methods for making a hypermutable plant comprising exposing at least one cell of said plant to an inhibitor of mismatch repair. The Euler reference allegedly describes the development of seedlings from seeds derived from rye pollen treated with chemicals such as camphor, anthracene, and benzoquinone that exhibit differences in leaf shape which "may be caused by mutation." There is no teaching or suggestion in the Euler reference of hypermutability of the chemically treated pollen grain. As explained in Example 3, there is a distinction between standard mutagens that induce genomic instability versus blockers of mismatch repair. It would not have been obvious to one of ordinary skill in the art in view of the Euler reference that exposure of a plant cell to an anthracene compound causes hypermutability as required by the present claims. Moreover, the Euler reference provides no method for distinguishing between a chemical inhibitor of mismatch repair and a general mutagen as provided in the present specification. As there is no teaching or suggestion in the Euler reference of the hypermutability of a plant cell caused by exposure to an anthracene compound, claims 1, 4-13, 72-82, and 84 are not obvious in view of that reference. Applicants respectfully request withdrawal of the rejection.

Claims 23, 26, and 68 encompass methods for generating a mutation in a gene of interest in a plant or yeast cell by exposing the cell to a chemical inhibitor of mismatch repair. Chemical inhibitors of mismatch repair make plant cells more susceptible to mutation through loss or impairment of the mismatch repair system. (Specification at page 10, lines 9-10.) The Euler reference allegedly describes the development of seedlings from seeds derived from rye pollen treated with chemicals such as camphor, anthracene, and benzoquinone that exhibit differences in leaf shape which "may be caused by mutation." There is no teaching or suggestion in the Euler reference of inhibition of mismatch repair in the chemically treated pollen grain. Moreover, the Euler reference provides no method for distinguishing between a chemical inhibitor of mismatch repair and a general mutagen as provided in the present specification. Additionally, there is no teaching or suggestion in the Euler reference of the enhanced rate of mutation that results upon combination treatment with a chemical inhibitor of mismatch repair and a standard mutagen as explained in Example 3 of the specification. As there is no teaching or suggestion in the Euler reference of chemical

inhibition of mismatch repair in a plant cell caused by exposure to an anthracene compound, claims 23, 26, and 68 are not obvious in view of that reference. Applicants respectfully request withdrawal of the rejection.

Claims 23, 68, and 70 are patentable over the Euler reference in combination with the Kimm or Laduca reference.

Claims 23, 68, and 70 are rejected under 35 U.S.C. § 103 for alleged obviousness over Euler taken together with Kimm *et al.* (*Korean J. Biochemistry*, 14:1-8, abstract (1982)) (“Kimm”) and Laduca (Diss, Abstr Int [B], 55, 11, 4741 (1995) Database CancerLit) (“Laduca”). Applicants respectfully assert that the Euler reference fails to teach chemical inhibition of mismatch repair as explained above. Moreover, it would not have been obvious to one of skill in the art that a combination of an anthracene compound with another standard mutagen would result in an *enhanced* rate of mutation. Neither the Kimm nor the Laduca references remedy the deficiencies of the Euler reference. Accordingly, Applicants respectfully assert that claims 23, 68, and 70 are patentable over the cited references. Withdrawal of the rejection is requested.

Claims 23, 24, and 26 are patentable over the LaVoie reference in combination with any one of the Krahn, Wigley, and Slaga references, further in view of the Chakravarti reference.

Claims 23, 24, and 26 are rejected under 35 U.S.C. 103 for alleged obviousness over the LaVoie reference taken together with any of Krahn *et al.* (*Mutation Res.*, 46:27-44 (1977)) (“Krahn”), Wigley *et al.* (*Int. J. Cancer*, 23:691-696 (1979)) (“Wigley”), or Slaga *et al.* (*Cancer Res.*, 38:1699-1704 (1978)) (“Slaga”), and in further view of Chakravarti *et al.* (*Proc. Natl. Acad. Sci. USA*, 92:10422-10426 (1995)) (“Chakravarti” or “the Chakravarti reference”). Applicants disagree with the rejection.

The LaVoie reference describes exposure of *Salmonella* bacteria and mouse skin cells to anthracene derivatives, and does not teach or suggest exposure of plant or yeast cells to anthracene derivatives. Similarly, the Krahn, Wigley, and Slaga references describe mutagenesis in Chinese hamster cell lines. None of these references, alone or in

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combination with the LaVoie reference, teaches or suggests exposure of plant or yeast cells to anthracene compounds. As such, all of the limits of the claimed invention are neither taught nor suggested. Moreover, one of ordinary skill in the art would not have referred to a study evaluating chemical mutagenesis in either bacteria or mammalian cells for the purpose of assessing generating a mutation in a gene of interest in plant cells. Thus, a *prima facie* case for obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 23, 26, 68, and 72-82 are patentable over the Euler reference taken together with the Zhang reference.

Claims 23, 26, 68, and 72-82 are rejected under 35 U.S.C. § 103 for alleged obviousness over Euler taken together with Zhang (U.S. Patent Application Publication No. 2002/0064879 A1) (“Zhang” or “Zhang reference”).

Applicants respectfully assert that the Euler reference fails to teach hypermutability and chemical inhibition of mismatch repair as previously explained. Moreover, it would not have been obvious to one of skill in the art that a combination of an anthracene compound with another standard mutagen would result in an *enhanced* rate of mutation. The Zhang reference fails to remedy the deficiencies of the Euler reference. Accordingly, Applicants respectfully assert that claims 23, 26, 68, and 72-82 are patentable over the cited references. Withdrawal of the rejection is requested.

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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully Submitted,

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